AWARD NUMBER: W81XWH-14-1-0109

TITLE: Combination Immunotherapy for the Treatment of High-Risk HER2-Positive Breast Cancer

PRINCIPAL INVESTIGATOR: Elizabeth A. Mittendorf, MD, PhD

CONTRACTING ORGANIZATION: The University of Texas MD Anderson Cancer Center
Houston, TX 77030

REPORT DATE: October 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2015	Annual Report	15 Sep 2014 - 14 Sep 2015

4. TITLE AND SUBTITLE
Combination Immunotherapy for the Treatment of High-Risk HER2-Positive Breast Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0109

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Elizabeth A. Mittendorf, MD, PhD

E-Mail: eamitten@mdanderson.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The University of Texas MD Anderson
Cancer Center
Houston, Texas 77030

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The objective of the proposed research is to complete a clinical trial evaluating the ability of the combination of trastuzumab and the HER2-derived vaccine nelipepimut-S administered with the immunoadjuvant GM-CSF in the adjuvant setting to prevent metastatic disease in high-risk HER2+ breast cancer patients. Completion of the trial will allow us to test our hypothesis that combination therapy with trastuzumab plus vaccination is a therapeutic modality with minimal toxicity that will prevent disease recurrence. The most significant accomplishment during this initial year of funding, was initiation of the clinical trial (specific aim #1). The study underwent review and approval by the USAMRMC ORP HRPO. The protocol was then IRB approved and activated as of 29 January 2015. The trial is currently accruing at 14 sites. Since trial initiation, a total of 60 eligible patients have been consented. Of those, 39 (65%) were of the appropriate HLA-type (HLA-A2 or A3 positive) to continue on study; the remaining 21 (35%) were considered screen failures. Of the qualified patients, 20 have been randomized and are on treatment; 10 are pending randomization, and 10 have withdrawn. Blood samples for immunologic monitoring are being collected in support of specific aims 2 and 3.

15. SUBJECT TERMS
Breast cancer, HER2-positive, immunotherapy, vaccines, NeuVax, clinical trial

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	8	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

1. Introduction

Despite advances in treatment, it is estimated that approximately 20% of women diagnosed with invasive breast cancer will recur and may eventually succumb to their disease. One group at high risk for recurrence are patients with HER2-positive tumors who do not achieve a pathologic complete response (pCR) after receiving chemotherapy plus trastuzumab in the neoadjuvant setting. Novel therapeutic strategies are therefore needed for patients failing to achieve a pCR. Our group has been investigating HER2-derived peptide vaccines that elicit a HER2-specific cytotoxic T lymphocyte (CTL) response. The vaccines have been administered to patients with any degree of HER2 expression (immunohistochemistry [IHC] 1+, 2+ or 3+) in the adjuvant setting to prevent disease recurrence. The vaccines are well tolerated with minimal toxicity. They stimulate a HER2-specific immune response and early phase clinical trials suggest clinical benefit with decreased recurrence rates in vaccinated patients compared with non-vaccinated controls. In patients with HER2-positive (= 3+ by IHC) tumors (n=50) that were vaccinated after receiving trastuzumab, there have been no recurrences after greater than 24 months follow-up. Based on these encouraging preliminary data where combination therapy virtually eliminated recurrences, we have designed an adequately powered clinical trial that will randomize patients that fail to achieve a pCR to receive maintenance trastuzumab alone (standard practice) or trastuzumab plus vaccine in the adjuvant setting. The primary *objective* of the proposed clinical trial is to assess the ability of the combination of trastuzumab and the HER2-derived peptide vaccine nelipepimut-S+GM-CSF given in the adjuvant setting to prevent recurrences in patients with HER2-positive breast cancer who were administered neoadjuvant chemotherapy plus trastuzumab and failed to achieve a pCR. Completion of the trial will allow us to test our *central hypothesis* that combination therapy with trastuzumab plus vaccination is a non-toxic therapeutic modality that will prevent disease recurrence in these patients thereby eliminating the mortality associated with HER2-positive metastatic breast cancer.

2. Keywords

Breast cancer
HER2-positive
Immunotherapy
Vaccine
NeuVax
Clinical Trial

3. Accomplishments

The focus of this project is to conduct an investigator initiated, multi-center, prospective, randomized, blinded, placebo-controlled phase II trial of trastuzumab + nelipepimut-S+GM-CSF versus trastuzumab + GM-CSF alone.

Major goals

Specific Aim #1. Determine the efficacy of nelipepimut-S+GM-CSF administered with trastuzumab in the adjuvant setting in patients with HER2-positive breast cancer not achieving a pCR after neoadjuvant chemotherapy plus trastuzumab.

In support of this project, a protocol entitled “Phase II trial of combination immunotherapy with nelipepimut-S + GM-CSF (NeuVax) and trastuzumab in high-risk HER2+ breast cancer patients” is being conducted.

Administrative/Regulatory

- MD Anderson Institutional Review Board Approval (proposed date of completion was pre-award)

    - Initial IRB approval obtained 18 Jun 2014
    - Following USAMRMC ORP HRPO review, IRB approval of revised protocol was obtained 5 Nov 2014.

- USAMRMC ORP HRPO Approval (proposed date of completion was pre-award)
    - Protocol was submitted for review on 4 Aug 2014
    - USAMRMC ORP HRPO review identified several revisions that focused primarily on identification of an independent research monitor as well as inclusion of language to indicate that USAMRMC ORP HRPO should be notified in cases of serious adverse events, can perform site visits, and have access to study-related records. These revisions were made and the protocol was re-submitted to USAMRMC ORP HRPO on 20 Sep 2014.
    - Revisions were accepted after which the protocol was re-submitted to the MD Anderson IRB where it was approved 5 Nov 2014. Notification of that approval was forwarded to the USAMRMC ORP HRPO which ultimately approved the protocol on 29 Dec 2014.

- Trial activation (proposed date of activation was 1 Oct 2014)
    - The trial was activated on 29 Jan 2015

- Site selection (proposed date of completion was pre-award, 30 Sep 2014)
    - The selection of the initial five sites was completed by 30 Sep 2014. In order to enhance accrual rate, we have now identified 14 sites, all of which have gotten IRB approval, completed their site initiation visit and begun screening for accrual to the study.

Trial accrual

It was anticipated that trial accrual would take 2 years to complete, Oct 2014 – Oct 2016. Enrollment began late January 2015. To date, 60 patients have consented. Based on HLA-A2/A3 status, 39 patients have qualified to continue on the study. Of these, 20 have been randomized and are currently on treatment, 10 are pending randomization and 10 have withdrawn. Based on the current rate of accrual, we project that we will complete accrual in approximately Oct 2016.

Specific Aim #2. Evaluate immunologic responses to nelipepimut-S+GM-CSF administered with trastuzumab.

- In vivo immune responses are being determined using a delayed type hypersensitivity (DTH) response performed pre-vaccination, one month after completion of the primary vaccination series and 6 months ± 2 weeks after the fourth booster inoculation. To date, pre-vaccination DTH has been completed on all randomized patients.
- In vitro immune responses will be assessed using a dextramer assay on PBMC obtained at multiple time points to include pre-vaccination (R0), after completion of the PVS (R6), prior to the first booster inoculation (RC6/B1), 1 month ± 1 week after the first booster inoculation (RB1) and 6 months ± 2 weeks following the final booster. To date, blood samples have been sent to Dr. Mittendorf's lab at MD Anderson where they have been processed and stored. Samples are being batched so that dextramer analyses at specific time points will be completed for all patients at the same time.

Specific aim #3. Obtain well annotated blood specimens from patients treated with trastuzumab + nelipepimut-S+GM-CSF or trastuzumab + GM-CSF alone to perform correlative studies.

- Blood samples are being drawn at designated timepoints. Specimens have been sent to Dr. Mittendorf's lab at MD Anderson where they have been processed and stored for use in performing correlative studies.

Opportunities for training and professional development

Nothing to report

Dissemination of results to communities of interest

Nothing to report

Plans during next reporting period to accomplish goals

During the next year we anticipate completing accrual to the clinical trial. To encourage trial accrual, we have instituted a monthly teleconference to communicate with investigators at all of the enrolling sites. As patients enroll on the study and move through their primary vaccination series and into their booster inoculations, we will continue to complete in vivo immune monitoring using the DTH reaction, as well as to draw blood for ex vivo immune monitoring and other correlative studies.

4. Impact

Impact on the development of the principal discipline(s) of the project

Nothing to report

Impact on other disciplines

Nothing to report

Impact on technology transfer

Nothing to report

Impact on society beyond science and technology

Nothing to report

5. Changes/Problems

Changes in approach

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Due to FDA approval of the drug pertuzumab in the neoadjuvant setting for patients with HER2-positive breast cancer, pCR rates have been higher than anticipated thereby decreasing the number of eligible patients. Therefore, in order to meet our accrual targets within the specified 2 year period, we increased the number of sites participating in this study to 14.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards and/or select agents

Nothing to report

6. Products

Publications, conference papers, and presentations

Nothing to report

Website(s) or other internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other products

Nothing to report

7. Participants & Other Collaborating Organizations

Individuals working on the project

Name	Elizabeth A. Mittendorf, MD, PhD
Project role	Principal Investigator
Nearest person month work	3
Contribution to project	Dr. Mittendorf is overseeing the entire project to include serving as the PI for the clinical trial
Funding support	N/A

Name	Holly Simmons, RN
Project role	Research Nurse
Nearest person month work	12
Contribution to project	Ms Simmons is serving as the lead research nurse for the trial. She is conducting all aspects of the study at MD Anderson and serves as a resource for research nurses at other enrolling sites.
Funding support	The current award supports 8 calendar months of salary support. The remaining 4 months is covered by an MD Anderson institutional award – High Impact Clinical Research Support Program (HI-CRSP).

Name	Anne Philips, PhD
Project role	Laboratory coordinator
Nearest person month work	6
Contribution to project	Dr. Philips is overseeing the collection, processing and storage or PBMC and serum samples. She is also

	overseeing collection of blood for HLA testing and coordinating with the CLIA-certified human flow lab to ensure that testing is completed and results are distributed to participating sites.
Funding support	N/A

Change in active other support of the PD/PI(s) or senior/key personnel since the last reporting period

Dr. Mittendorf has had the following changes in other support:

- Grants closed
    - Cyclin E: A novel target for immunotherapy (National Cancer Institute: R00CA13324-01)
    - Evaluation of PD-L1 as a target for immunotherapy in inflammatory breast cancer (MD Anderson Cancer Center Morgan Welch Inflammatory Breast Cancer Program Seed Grant)
- New active grant
    - Immunologic aspects of triple negative breast cancer (TNBC) and the effects of neoadjuvant systemic therapy (MD Anderson Sister Institution Network Fund)

Other organizations involved as partners

- Galena Biopharma
  2000 Crow Canyon Place, Suite 380
  San Ramon, CA 94583

  Galena Biopharma provides the study drug as well as funding to Cancer Insight (see below) for their role in the conduct of this study.

- Cancer Insight, LLC
  600 Navarro Street, Suite 500
  San Antonio, TX 78205

  Cancer Insight oversees conduct of the study at sites other than MD Anderson. At these sites, they are responsible for site set-up, training and initiation, study drug distribution, inventory, and accountability; data collections and management through electronic data capture; site management, monitoring and auditing; and financial management through contracting and pass-through cost distribution.

8. Special Reporting Requirements

Not applicable

9. Appendices

None